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(54) Title: SYNERGISTIC INHIBITION OF HIV-1 INFECTION USING A NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR AND ANTI-HIV-1 ANTIBODIES

(57) Abstract

Disclosed is a composition of nucleoside reverse transcriptase inhibitors, preferably AZT, in combination with neutralizing anti-HIV-1 antibodies, to treat or prevent HIV-1 infection. Polyclonal antibodies or monoclonal antibodies which target a neutralizing domain of gp120, such as the V3 region, the C4 region, the V2 loop, or the CD4 binding domain can be used. The more preferred antibodies are those targeting the principal neutralizing determinant of the V3 region. The most preferred anti-gp120 monoclonal antibody is AIDS-439. This composition has been found to have a synergistic effect in neutralizing HIV-1 infectivity.

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Synergistic Inhibition of HIV-1 Infection Using a Nucleoside Reverse Transcriptase Inhibitor and Anti-HIV-1 Antibodies

Field of the Invention

The invention relates to treatment of HIV-1 infection and HIV-1 disease.

Background of the Invention

It is well known that AIDS is one of the most serious health problems facing the world. Monoclonal antibodies which bind to a neutralizing epitope of the human immunodeficiency virus type 1 ("HIV-1") -- the virus which causes AIDS -- have been suggested for both treating and preventing HIV-1 infection. Most neutralizing anti-HIV-1 antibodies target specific regions of the envelope glycoproteins gp120 and gp41. Some of these regions are the principal neutralizing determinant in the V3 region, the C4 region, the V2 loop, and the CD4-binding domain. Monoclonal antibodies which target the principal neutralizing determinant ("PND") have been shown to protect from infection in animal models.

The anti-HIV-1 antibodies referred to prevent infection of T cells with the virus. The T cells are critical to the proper functioning of the immune system. When HIV-1 infects human T cells, it ultimately destroys these cells by lysing them. As the

number of T cells declines, the victim's immune system is increasingly compromised, and opportunistic infections and tumors which are characteristic of AIDS result. The invariable outcome of the infection is the death of the victim, usually as a direct result of one or more of these complications.

A number of nucleoside reverse transcriptase inhibitors including Zidovudine™ (also known as "AZT"), dideoxyinosine ("ddI"), and dideoxycytidine ("ddC") are approved for use in treatment of HIV-disease. There are also indications, particularly for AZT, that these inhibitors can prevent infection of newborn whose mothers are HIV-1 seropositive. This mode of infection is known as vertical transmission.

Anti-HIV monoclonal antibodies are also intended for use in preventing vertical transmission, or otherwise protecting persons who are exposed to the virus. Such exposure can occur, for example, when a hospital worker is accidentally punctured with an HIV-1 contaminated needle or other sharp object, or through unprotected sexual contact with an infected person. Administering anti-HIV monoclonal antibodies to inhibit progression of disease or to prevent infection is known as passive immunization.

To date, no one has shown a synergistic effect in inhibiting HIV-1 infection through a combination of anti-HIV-1 monoclonal

antibodies and a nucleoside reverse transcriptase inhibitor.

Summary of the Invention

The invention includes the use of nucleoside reverse transcriptase inhibitors, preferably AZT, in combination with one or more neutralizing anti-HIV-1 antibodies, to treat or prevent HIV-1 infection. Polyclonal or monoclonal antibodies can be used, with the preferred antibodies being those which target a neutralizing domain of gp120 or gp41, and the more preferred being those targeting the PND or gp120. The most preferred anti-gp120 monoclonal antibody is AIDS-439, which is a genetically engineered chimeric mouse/human monoclonal antibody with human IgG1 constant regions and variable regions corresponding to the murine monoclonal antibody BAT123. A transfectoma cell line producing AIDS-439 is on deposit at the American Type Culture Collection ("ATCC"), 12301 Parklawn Drive, Rockville Maryland 20853 under Accession Number CRL 10499. A hybridoma cell line producing BAT123 is on deposit at the ATCC under Accession Number HB 10438.

It has been discovered in *in vitro* tests that when certain nucleoside reverse transcriptase inhibitors are used in combination with neutralizing anti-HIV-1 monoclonal antibodies, there is a synergistic effect, resulting in greater viral neutralization than

would be expected merely by adding the dosages of the products together. The same effect is likely to occur if neutralizing polyclonal antibodies are used, particularly if such polyclonals bind to the PND.

In addition to use in therapy or prevention of HIV-1 infection, neutralizing anti-HIV-1 antibodies, polyclonal and monoclonal, can also be used to assay a biological fluid sample for HIV-1 virions or for HIV-1-infected cells, or to quantify the concentration of HIV-1 or of infected cells, present in a biological fluid. This is useful for diagnosis of HIV-1 infection and detection of HIV-1 contamination in a culture or another sample. These antibodies can be used in standard assay formats, such as the ELISA format or the immunofluorescence format described below.

Description of Making and Using the Invention

As noted above, the invention includes the use of nucleoside reverse transcriptase inhibitors, preferably AZT, in combination with neutralizing anti-HIV-1 antibodies, to treat or prevent HIV-1 infection. Preferred nucleoside reverse transcriptase inhibitors are AZT, ddI, and ddC. The dosage ranges for these inhibitors are all readily available from the pharmacopeias, as these products are approved for sale. The recommended dosages should be used when practicing the

invention, although other dosages which do not result in toxicity and which result in synergistic neutralization are also acceptable.

The neutralizing anti-HIV-1 antibodies for use in the invention are preferably those targeting the PND, the C4 region, the V2 loop, or the CD4-binding domain. A number of such antibodies are known and available. AIDS-439 targets the PND. G3-519, G3-508 and G45-60 (the cells lines producing them are on deposit at the ATCC under Accession Numbers HB 10747, HB 10748, and HB 10749, respectively) target the C4 region. BAT 085, G3-136 and G3-4 (the cell lines producing them are on deposit at the ATCC under Accession Numbers HB 11118, HB 10932, and HB 10733, respectively) target the V2 loop. There are also a number of other monoclonal antibodies which target these same regions, or otherwise neutralize HIV-1, and which can be used in the invention.

The recommended dosage for the monoclonal antibodies can be estimated based on *in vitro* studies and animal model studies. To perform this extrapolation, one determines the dosage in animal models (such as the hu-PBL-SCID mouse) which is effective in protecting the animals from HIV-1 infection, when they are administered the same dose of HIV-1. Then one multiplies this dosage by the ratio of the mass of the human over

that of the animal. This provides the initial estimate of the dosage to be administered to the human. From there, a more precise determination is made by administering a range of doses to a number of different test subjects. An example of how an animal model experiment in hu-PBL-SCID mice can be carried out is set forth below.

Example 1: Protection of hu-PBL-SCID Mice from Infection

A study was made of the ability of two monoclonal antibodies of the invention, BAT123 and AIDS-439, to protect hu-PBL-SCID mice from infection by HIV-1. The protocol for this study was as follows.

SCID mice were reconstituted by intraperitoneal (i.p.) injection of 2×10^7 human peripheral blood lymphocytes (PBL). After 14 days, the reconstituted mice were checked for human immunoglobulin. To be used in the study, the reconstituted hu-PBL-SCID mice were required to show a human immunoglobulin level of at least 10 μg/ml in their sera.

The hu-PBL-SCID mice for use in the study were divided into three groups with six mice in each group. One group was a control group, and received the irrelevant immunoglobulin PNTU. Another group received BAT123 and the remaining group received AIDS-439. All antibodies were injected i.p. at a dose of 40 mg/kg

of animal weight. One hour after antibody administration, the animals were inoculated i.p. with HIV-1_{IIIB}, at a dose adequate to infect at least 80% of the animals, as calculated based on a prior virus titration in other hu-PBL-SCID mice. This dosage is 10 times the dosage needed to infect 50% of the animals.

Serum samples were taken from the animals at selected intervals in order to study the pharmacokinetics of the injected antibodies. The animals were sacrificed three weeks after inoculation and their spleen cells and peritoneal lavage were cultured for HIV-1 for four weeks. Cells from the peritoneal lavage and spleen cells were analyzed for HIV-1 infection by co-cultivation, and only spleen cells were analyzed by PCR.

As determined using a co-cultivation p24 antigen assay of both the peritoneal lavage and the spleen cells, and by PCR of spleen cells, none of the 12 hu-PBL-SCID mice which received BAT123 and AIDS-439 showed any HIV-1 infection. Five out of the six control mice showed infection of their spleen cells as determined by co-cultivation, and two of the five showed infection by PCR. Only one control animal showed infection of the cells from the peritoneal lavage.

It was not unexpected that only one control animal showed infection of cells from the peritoneal lavage, as far fewer of the

peritoneal lavage cells were cultured. Further, it was not unexpected that fewer control animals showed infection using PCR as compared with co-cultivation, because fewer cells were analyzed using PCR. The results from the co-cultivation, showing five of six control animals infected, are believed to be more sensitive than the PCR results.

A range of the same dosages of AIDS-439 (40 mg/kg of animal weight) could be used in humans, in beginning the determination of the appropriate dosage to use. The same procedure could be used to determine the appropriate dosage of other anti-HIV-1 antibodies.

Example II: Safety and Tolerability of AIDS-439

A clinical trial was conducted in 12 male CDC stage IV AIDS patients to determine the safety and tolerability of the AIDS-439, and whether it had biological activity *in vivo*.

Patients were screened from the closely monitored AIDS patients at the University Hospital of Zurich. Twelve male AIDS patients selected were above age 18. Each had $CD4^+$ lymphocyte counts of 10-230/mm^3 with proven viremia at CDC stage IV clinical status, i.e., up to 3 opportunistic C1 or C2 type infections with a life expectancy of at least 6 months. All patients were withdrawn from AZT treatment four to six weeks before the trial

began.

These patients were HIV-1 antigenemic (positive by HIV-1 antigen assays and tissue culture infectious dose (TCID) assays). These patients were divided into three groups and entered into a dose schedule as described in Table I. The gp120 of patient HIV-1 isolates from eight patients in Groups 2 and 3 were tested reactive with AIDS-439 in a specially designed capture ELISA.

After appropriate data evaluation within 5 days following the infusion of the highest dose of 200 mg to Group 3 patients, a decision was made to continue the trial with up to eight doses of AIDS-439 identical to the highest dose for each of the three groups, to be given three weeks apart (see Table I).

The 12 selected patients were carefully evaluated, beginning 6-8 weeks before the trial. Monitoring and recording activities for each patient included a medical history, clinical examination, and various laboratory tests, including hematology, clinical chemistry, general immunology, HIV antigen test, HIV-1 viremia, special immunology, and urinalysis.

Follow-up clinical and laboratory evaluation was scheduled at regular intervals during treatment. HIV-1 antigenemia was monitored by the Abbott HIV Ag test and HIV viremia was monitored by tissue culture for TCID, PCR, and branched DNA

amplification techniques. The pharmacokinetics of AIDS-439 were determined using a double-antibody capture ELISA employing an anti-idiotypic antibody to AIDS-439. Emergence of human anti-antibodies to AIDS-439 in patients also was examined.

$CD4^+$, $CD3^+$,and $CD8^+$cells from peripheral blood were enumerated with use of specific monoclonal antibody reagents and flow cytometry. All laboratory work complied with good clinical practices.

Clinical and laboratory analysis data in combination with the weekly physical examinations were the basis for review of the clinical status of each patient throughout the trial. Good tolerability was defined as lack of subjective or objective symptoms following administration of AIDS-439.

TABLE I
AIDS-439 DOSE SCHEDULE

	Group 1		Group 2		Group 3	
Infusion	n = 4	mg	n = 4	mg	n = 4	mg
1°	4	1	4	10	4	25
2°	4	50	4	100	4	200
3°	3*	50	4	100	4	200
4°	3	50	3*	100	4	200
5°	3	50	3	100	4	200
6°	2*	50	3	100	4	200
7°	2	50	3	100	4	200
8°	2	50	3	100	4	200

* indicates a patient dropping out

AIDS-439 was well tolerated, even up to a cumulative dose of 1,425 mg over 170 days. However, one patient reported tiredness at an interim stage in the trial. Among the patients receiving the highest dose of AIDS-439 (Group 3), all of them showed stabilization of body weight and all survived for the entire 170 day trial period. This indicates that AIDS-439 can be safely administered at a dose up to at least 200 mg per administration, cumulatively over several weeks. Such dosages can be used in the present invention. The same protocol detailed above can be used to determine the safe and effective dosage of other anti-HIV antibodies. In summary, one uses several different dosages in

various patients and monitors their reaction and their clinical response over a period of time.

Example III: Synergy in Inhibition of HIV-1 Infection by a Combination of AZT and AIDS-439

The following is an analysis of the inhibition of HIV-1 IIIB infection of CEM-SS cells (a human T cell line) by a combination of AZT and AIDS-439. Progressively increasing dosages of AIDS-439 and AZT were added to a culture of CEM-SS cells, a human T cell line known to be subject to HIV-1 infection. An infectivity assay was then performed on the CEM-SS cells, using the method of Nara, P. et al., *AIDS Res. Human Retroviruses* 3:283-302 (1987). The results are set forth in Table II below.

TABLE II

Percent Inhibition of HIV-1IIIB Infection of CEM-SS Cells by a combination of AZT and AIDS-439

AZT (μM)	AIDS-439 (μg/ml)			
	0	0.039	0.078	0.156
0	0	1	19	51
0.0031	0.1	15		
0.0063	1		47	
0.0125	26			75
0.0250	41			
0.050	58			
0.10	69			
0.20	77			
0.40	90			

AZT (μM)	AIDS-439 (μg/ml)				
	0.313	0.625	1.250	2.50	5.0
0	68	89	94	97	98
0.0031					
0.0063					
0.0125					
0.0250	91				
0.050		98			
0.10			99		
0.20				99	
0.40					99

A synergy analysis was then carried out on the results of the AZT and AIDS-439 combination. This analysis was conducted by first determining CI, combination indices, which were

calculated based on the median-effect equation for mutually non-exclusive interaction (for drugs with distinct mechanisms of action) as described by Chou and Talalay, *Adv. Enzyme Regul.* 22:27-55 (1984). For CI <1, this indicates synergism; for CI $= 1$, the effect is additive; and for CI >1, this indicates antagonism. IC_{50} is the median inhibitory concentration (μg/ml), r is the correlation coefficient as determined from the median-effect plot, and m is the slope of the plot. The results of this analysis are set forth in Table III below.

TABLE III

Synergy analysis of AZT and AIDS-439 combinations against HIV-1IIIB infection of CEM-SS cells by syncytium-formingassay

Inhibitor	Parameter		
	m	IC_{50}	r
AIDS-439	1.61	0.257	0.96
AZT	1.69	0.0174	0.92
AIDS-439/AZT (46.8:1)+	1.71	0.089	0.99

+ concentration ratio, μg/ml

Inhibitor	CI at % Inhibition		
	50	70	90
AIDS-439			
AZT			
AIDS-439/AZT (46.8:1)+	0.48	0.47	0.45

+ concentration ratio, μg/ml

This synergy analysis in Table III shows that there is a synergistic effect from a combination of AZT and AIDS-439. The same synergistic effect is expected from other combinations of neutralizing anti-HIV-1 antibodies and nucleoside reverse transcriptase inhibitors.

Example IV: Use of Antibodies for Detection or Quantitation of HIV-1 Virions or Infected Cells

As noted above, anti-HIV-1 antibodies, monoclonal and

polyclonal, can be used for detection or quantitation of HIV-1 virions or infected cells. A protocol for carrying this out is described below.

(i) Detecting HIV-1 virions and HIV-1 gp120 in specimens

The antibodies of the invention, either alone or in combination, can be immobilized on inert solid matrices or magnetic beads, either directly or indirectly through a cross-linking agent or a specific binding agent (e.g. protein A, goat anti-mouse IgG, or goat anti-human IgG). The biological fluid test samples are then incubated with the antibody-coated matrices. HIV-1 virions or gp120 reactive with the antibodies will bind to the matrices. The bound virions or gp120 can then be detected with either monoclonal or polyclonal anti-HIV-1 antibodies, which can then be reacted with enzyme-linked secondary detecting antibodies for quantitation based on color reaction. Alternatively, the captured virions can be detected by other means, e.g. fluorescence, chemiluminescence, or PCR.

(ii) Detecting HIV-1-Infected Cells in a Specimen

The monoclonal antibodies of the invention can be used to detect and to quantitate the HIV-1-infected cells in patient blood samples by direct or indirect immunofluorescence procedures. The

protocol is well-known by those skilled in the art, and is described specifically in U.S. Application Serial No. 07/950,571.

The terms, expressions and examples herein are exemplary only and not limiting, and those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. All such equivalents are intended to be encompassed by the following claims.

What Is Claimed Is:

1. A composition comprising neutralizing anti-HIV-1 antibodies and a quantity of nucleoside reverse transcriptase inhibitor.

2. The composition of claim 1 wherein the neutralizing anti-HIV-1 antibodies are monoclonal or polyclonal.

3. The composition of claim 2 which specifically bind to the principal neutralizing determinant of the V3 loop, the C4 region, the CD4 binding domain, or the V2 loop of HIV-1 gp120.

4. The composition of claim 1 wherein the nucleoside reverse transcriptase inhibitor is Zidovudine™, dideoxyinosine, or dideoxycytidine.

5. A composition of AIDS-439 and Zidovudine™.

6. A composition of the chimeric antibody form of G3-519, having a murine variable region and a human constant region, and Zidovudine™.

7. A method of treating or preventing HIV-1 infection comprising administering the composition of any of claims 1-4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/03169

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/70, 39/42; C07H 19/06; C07K 16/10.
US CL :424/133.1, 148.1; 514/8, 51; 530/387.3, 388.35; 536/28.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/133.1, 148.1; 514/8, 51; 530/387.3, 388.35; 536/28.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CLINICAL AND EXPERIMENTAL IMMUNOLOGY, Vol. 88, issued 1992, Fahey et al., "Status of immune-based therapies in HIV infection and AIDS," pages 1-5, see entire document.	1-7
A	BIO/TECHNOLOGY, Vol. 12, issued February 1994, Fox, J.L., "No Winners Against AIDS," page 128, see entire document, particularly column 3, last paragraph.	1-7
X -- Y	WO, A, 9207878 (TILLEY ET AL) 14 MAY 1992, page 22, lines 8-13.	1-4, 7 --- 5-6
Y	US, A, 5,086,044 (RIDEOUT ET AL.) 04 FEBRUARY 1992, see Abstract and col. 4, lines 24-35.	1-7

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 14 JUNE 1995	Date of mailing of the international search report 29 JUN 1995
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passage.	Relevant to claim No.
Y	US, A, 5,234,913 (FURMAN ET AL.) 10 AUGUST 1993, see Abstract.	1-7
Y	US, A, 5,245,015 (FUNG ET AL.) 14 SEPTEMBER 1993, Col. 11, lines 25-31.	1-7
Y	US, A, 5,266,478 (CHANG ET AL.) 30 NOVEMBER 1993, see Figure 1.	1-7
Y	THE JOURNAL OF IMMUNOLOGY, Vol. 143, No. 12, issued 15 December 1989, Liou et al., "A Chimeric Mouse-Human Antibody That Retains Specificity For HIV gp120 And Mediates The Lysis Of HIV-Infected Cells," pages 3967-3975, see entire document.	1-7
Y	AIDS RESEARCH AND HUMAN RETROVIRUSES, Vol. 9, Supplement 1, issued October 1993, Safrit et al., "Protection of hu-PBL-SCID Mice From Infection With Human Immunodeficiency Virus Type 1 Through Passive Transfer Of A Monoclonal Antibody Directed Against The Third Variable Region Of The Envelope gp120," page s78, see Abstract.	1-7
Y	CLINICAL MICROBIOLOGY REVIEWS, Vol. 5, No. 2, issued April 1992, Bean, B., "Antiviral Therapy: Current Concepts and Practices," pages 146-182, see page 166, first column, first full paragraph.	1-7

INTERNATIONAL SEARCH REPORT

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

Group I, claim(s)1-5 and 7, drawn to compositions containing antibodies and nucleoside reverse transcriptase inhibitors.
Group II, claim(s) 6, drawn to a second composition containing antibody G3-519 and ZIDOVUDINE.
The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the antibody of group II differs in its structure and immunological activity from the AIDS-439 antibody of Group I and are not so linked by a special technical feature under PCT Rule 13.1 as to form a single general inventive concept.